Micromixer

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TITLE: In situ activation of microcapsules

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CLAIMS:

What is claimed is:

1. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal liquids, wherein each internal liquid is immiscible with the other internal liquids, and all of the internal liquids are enclosed together in a single polymer shell, a drug precursor associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source in an amount effective to promote physical mixing of the immiscible liquid phases and to increase the activation kinetics of activation of the drug precursor.

2. The method of claim 1, wherein one of said internal liquid phases is an aqueous phase and one of said internal liquid phases is a hydrocarbon or oil phase.

3. The method of claim 2, wherein said aqueous phase is in contact with the polymer membrane.

4. The method of claim 2, wherein said hydrocarbon or oil phase is in contact with the polymer membrane.

5. The method of claim 3, wherein the drug precursor is more soluble in the hydrocarbon or oil phase than in the aqueous phase and the activated drug is more soluble in the aqueous phase than in the hydrocarbon or oil phase.

6. The method of claim 4, wherein the drug precursor is more soluble in the aqueous phase than in the hydrocarbon or oil phase and the activated drug is more soluble in the hydrocarbon or oil phase than in the aqueous phase.

7. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal immiscible liquid phases enclosed in a polymer shell, a drug precursor

associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source in an amount effective to promote physical mixing of the immiscible liquid phases and to increase the activation kinetics of activation of the drug precursor,

wherein one of said internal liquid phases is an aqueous phase and one of said internal liquid phases is a hydrocarbon or oil phase,

wherein said aqueous phase is in contact with the polymer membrane,

wherein the drug precursor is more soluble in the hydrocarbon or oil phase than in the aqueous phase and the activated drug is more soluble in the aqueous phase than in the hydrocarbon or oil phase,

wherein the pair consisting of said drug precursor and drug is chosen from the group consisting of papaverine and papaverine HCl, genoscopolamine and scopolamine, hematoporphyrin and dihematoporphyrin ester, and sulfamerazine sulfate and 2-sulfanilamido-4-methylpyrimidine.

8. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal immiscible liquid phases enclosed in a polymer shell, a drug precursor associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source in an amount effective to promote physical mixing of the immiscible liquid phases and to increase the activation kinetics of activation of the drug precursor,

wherein one of said internal liquid phases is an aqueous phase and one of said internal liquid phases is a hydrocarbon or oil phase,

wherein said hydrocarbon or oil phase is in contact with the polymer membrane,

wherein the drug precursor is more soluble in the aqueous phase than in the hydrocarbon or oil phase and the activated drug is more soluble in the hydrocarbon or oil phase than in the aqueous phase,

wherein the pair consisting of the drug precursor and the drug is chosen from the group consisting of floxuridine and 5-fluorouracil, cocaine hydrochloride and cocaine base, and estrone and estradiol.

9. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal immiscible liquid phases enclosed in a polymer shell, a drug precursor associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source that causes the precursor to assume an active state,

wherein the pair consisting of said drug precursor and the drug is chosen from the group consisting of dehydrocholesterol and vitamin D.sub.3, testosterone acetate and testosterone, ergosterol and vitamin D.sub.2, nitromethane and 1-methyl-2(1-hydroxy-1 methylethyl) diazene, and .alpha., .alpha.-dinitroketone and a diketone.

10. A micromixer useful for mixing two or more immiscible liquid phases contained in the micromixer comprising:

a microcapsule comprising two or more immiscible internal liquid phases enclosed in a polymer shell and a radiant energy source effective to generate liquid flow within the microcapsule,

said microcapsule formed by a method comprising:

formulating a first phase comprising a first solvent, a first polymer soluble in said first phase and immiscible in a second phase, a co-solvent, oil, and water;

formulating said second phase immiscible with said first phase, said second phase comprising a second solvent, a second polymer soluble in said second phase and immiscible in said first phase, a surface active agent, and a salt;

said surface active agent having a hydrophilic/lipophilic balance value greater than that of said first polymer;

said second polymer having a hydrophilic/lipophilic balance value lower than that of said surface active agent;

creating an interface between said first and second phases in a manner that limits fluid shear, and

maintains adsorptive surface characteristics at said interface.

11. A composition comprising a drug or drug precursor contained in a microcapsule comprising two or more concentric, immiscible internal liquid phases enclosed in a polymer shell, wherein a first of said internal liquid phases is in contact with said polymer shell, and wherein a second of said internal liquid phases is separated from said polymer shell by said first internal liquid phase, and further wherein said drug or drug precursor is associated with said second internal liquid phase,

wherein said microcapsule is formed by a method comprising:

formulating a first phase comprising a first solvent, a first polymer soluble in said first phase and immiscible in a second phase, a co-solvent, oil, and water;

formulating said second phase immiscible with said first phase, said second phase comprising a second solvent, a second polymer soluble in said second phase and immiscible in said first phase, a surface active agent, and a salt;

said surface active agent having a hydrophilic/lipophilic balance value greater than that of said first polymer;

said second polymer having a hydrophilic/lipophilic balance value lower than that of said surface active agent;

creating an interface between said first and second phases in a manner that limits fluid shear, and

maintains adsorptive surface characteristics at said interface.

12. The method of claim 9, wherein said drug precursor is dehydrocholesterol and the drug is vitamin D.sub.3.

13. The method of claim 9, wherein said drug precursor is testosterone acetate and the drug is testosterone.

14. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal immiscible liquid phases enclosed in a polymer shell, a drug precursor associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source in an amount effective to promote physical mixing of the immiscible liquid phases and to increase the activation kinetics of activation of the drug precursor,

wherein the microcapsule also contains a radiocontrast media.

15. The method of claim 14, wherein the radiocontrast media is a halogenated oil.

16. The method of claim 15 wherein the radiocontrast media is an oil selected from the group consisting of halogenated poppy seed oil, cotton seed oil, soybean oil, safflower oil, corn oil, sesame seed oil, and canola oil.

17. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal immiscible liquid phases enclosed in a polymer shell, a drug precursor associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source in an amount effective to promote physical mixing of the immiscible liquid phases and to increase the activation kinetics of activation of the drug precursor,

wherein the drug precursor is a proenzyme.

18. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal immiscible liquid phases enclosed in a polymer shell, a drug precursor associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source in an amount effective to promote physical mixing of the immiscible liquid phases and to increase the activation kinetics of activation of the drug precursor,

wherein the drug precursor is selected from the group consisting of a pro-thrombolytic enzyme, a pro-urokinase and a pro-tissue plasminogen activator.

19. The method of claim 1 wherein the energy source is selected from the group consisting of ultraviolet light, near infrared light, an electromagnetic field, radiofrequency, and microwave radiation.

20. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal immiscible liquid phases enclosed in a polymer shell, a drug precursor associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source in an amount effective to promote physical mixing of the immiscible liquid phases and to increase the activation kinetics of activation of the drug precursor,

wherein the energy is near infrared light of about 700-900 nanometer wavelength.

21. A method of in situ activation of a drug comprising:

providing a micro capsule wherein the microcapsule comprises two or more internal immiscible liquid phases enclosed in a polymer shell, a drug precursor associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source in an amount effective to promote physical mixing of the immiscible liquid phases and to increase the activation kinetics of activation of the drug precursor,

wherein the energy is ultraviolet light of about 220-390 nanometer wavelength.

22. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal immiscible liquid phases enclosed in a polymer shell, a drug precursor

associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source in an amount effective to promote physical mixing of the immiscible liquid phases and to increase the activation kinetics of activation of the drug precursor,

further defined as comprising administering said microcapsules to a subject, allowing said microcapsules to reach a target site and applying said energy to the subject.

23. The method of claim 22, wherein the location of the microcapsules is detected by a radio image.

24. The method of claim 22, wherein administration is intraarterial, intravenous or intraperitoneal.

25. The method of claim 22, wherein the microcapsules at least partially occlude a blood vessel.

26. The method of claim 22, wherein the energy is applied using an intravascular device.

27. The method of claim 26, wherein the intravascular device is a catheter.

28. The method of claim 26, wherein the energy is applied via a fiber optic conductor.

29. The method of claim 26, wherein the energy is applied via an electromagnetic transducer contained in an intravascular device.

30. The method of claim 1, wherein the microcapsule is from about 1 to about 500 microns in diameter.

31. The method of claim 1, wherein the microcapsule is from about 300 to about 500 microns in diameter.

32. The method of claim 1, wherein the microcapsule is from about 50 to about 300 microns in diameter.

33. The method of claim 1, wherein the microcapsule is from about 30 to about 50 microns in diameter.

34. The method of claim 1, wherein the microcapsule is from about 20 to about 30 microns in diameter.

35. The method of claim 1, wherein the microcapsule is from about 1 to about 20 microns in diameter.

36. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal immiscible liquid phases, wherein neither internal immiscible liquid phase is enclosed separately by a polymer shell but wherein the internal immiscible liquid phases are enclosed together in a single polymer shell, a drug precursor associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source that causes the precursor to assume an active state.

37. The method of claim 36, wherein the drug precursor is activated by a oxidation, a reduction, a hydrolysis or a dehydrogenation reaction.

38. A composition comprising a drug or drug precursor contained in a microcapsule consisting of two or more concentric, immiscible internal liquid phases, wherein neither internal immiscible liquid phase is enclosed separately

by a polymer shell but wherein the internal immiscible liquid phases are enclosed together in a single polymer shell, wherein a first of said internal liquid phases is in contact with said polymer shell, and wherein a second of said internal liquid phases is separated from said polymer shell by said first internal liquid phase, and further wherein said drug or drug precursor is associated with said second internal liquid phase.

39. The composition of claim 38, wherein said first internal liquid phase is an aqueous phase.

40. The method of claim 9, wherein said drug precursor is ergosterol and the drug is vitamin D.sub.2.

41. The method of claim 9, wherein the drug precursor is nitromethane and the drug is 1-methyl-2(1-hydroxy-1 methylethyl) diazene.

42. The method of claim 9, wherein the drug precursor is .alpha., .alpha.-dinitroketone and the drug is a diketone.

43. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal immiscible liquid phases enclosed in a polymer shell, a drug precursor associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source that causes the precursor to assume an active state,

wherein the microcapsule also contains a radiocontrast media.

44. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal immiscible liquid phases enclosed in a polymer shell, a drug precursor associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source that causes the precursor to assume an active state,

wherein the microcapsule contains the radiocontrast media a halogenated oil.

45. The method of claim 44, wherein the radiocontrast media is selected from the group consisting of halogenated poppy seed oil, cotton seed oil, soybean oil, safflower oil, corn oil, sesame seed oil, and canola oil.

46. The method of claim 36, wherein the energy source is ultraviolet light or near infrared light.

47. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal immiscible liquid phases enclosed in a polymer shell, a drug precursor associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source that causes the precursor to assume an active state,

wherein the energy source is near infrared light of about 700-900 nanometer wavelength.

48. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal immiscible liquid phases enclosed in a polymer shell, a drug precursor associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source that causes the precursor to assume an active state,

wherein the energy source is ultraviolet light of about 220-390 nanometer wavelength.

49. A method of in situ activation of a drug comprising:

providing a microcapsule wherein the microcapsule comprises two or more internal immiscible liquid phases enclosed in a polymer shell, a drug precursor associated with at least one internal liquid phase; and

exposing the microcapsule to an energy source that causes the precursor to assume an active state,

further defined as comprising administering said microcapsules to a subject, allowing said microcapsules to reach a target site and applying said energy to the subject.

50. The method of claim 49, wherein the location of the microcapsules is detected by a radio image.

51. The method of claim 49, wherein administration is intraarterial, intravenous or intraperitoneal.

52. The method of claim 49, wherein the microcapsules at least partially occlude a blood vessel.

53. The method of claim 49, wherein the energy is applied using an intravascular device.

54. The method of claim 53, wherein the intravascular device is a catheter.

55. The method of claim 53 wherein the energy is applied via a fiber optic conductor.

56. The method of claim 53 wherein the energy is applied via an electromagnetic transducer contained in an intravascular device.

57. The method of claim 36, wherein the microcapsule is from about 1 to about 500 microns in diameter.

58. The method of claim 36, wherein the microcapsule is from about 300 to about 500 microns in diameter.

59. The method of claim 36, wherein the microcapsule is from about 50 to about 300 microns in diameter.

60. The method of claim 36, wherein the microcapsule is from about 30 to about 50 microns in diameter.

61. The method of claim 36, wherein the microcapsule is from about 20 to about 30 microns in diameter.

62. The method of claim 36, wherein the microcapsule is from about 1 to about 20 microns in diameter.

63. A micromixer useful for mixing two or more immiscible liquid phases contained in the micromixer comprising:

a microcapsule consisting of two or more immiscible internal liquid phases, wherein neither internal immiscible liquid phase is enclosed separately by a polymer shell but wherein the internal immiscible liquid phases are enclosed together in a single polymer shell and a radiant energy source effective to

generate liquid flow within the microcapsule.

64. The micromixer of claim 63, wherein said internal liquid phases include an aqueous phase and a hydrocarbon or oil phase.

65. The micromixer of claim 63, wherein the energy source is selected from the group consisting of a source of ultraviolet light, an electromagnetic field, a radiofrequency, or microwave energy.

66. A micromixer useful for mixing two or more immiscible liquid phases contained in the micromixer comprising:

a microcapsule comprising two or more immiscible internal liquid phases enclosed in a polymer shell and a radiant energy source effective to generate liquid flow within the microcapsule,

wherein the energy source is a source of ultraviolet light at 220 to 390 nanometers wavelength.

67. The micromixer of claim 64, wherein said micromixer comprises a reactant associated with an aqueous phase and a different reactant associated with a hydrocarbon or oil phase, wherein said reactants produce a chemical reaction upon contact and wherein said mixing increases the reaction kinetics of the reaction.

68. The composition of claim 38, wherein said first internal liquid phase is a hydrocarbon or oil phase.

69. The composition of claim 38, wherein said composition is contained in a light protective container.

70. The method of claim 7, wherein said drug precursor is papaverine and the drug is papaverine HCl.

71. The method of claim 7, wherein said drug precursor is genoscopolamine and the drug is scopolamine.

72. The method of claim 7, wherein said drug precursor is hematoporphyrin and the drug is dihematoporphyrin ester.

73. The method of claim 7, wherein said drug precursor is sulfamerazine sulfate and the drug is 2-sulfanilamido-4-methylpyrimidine.

74. The method of claim 8, wherein the drug precursor is floxuridine and

the drug is 5-fluorouracil.

75. The method of claim 8, wherein the drug precursor is cocaine hydrochloride and the drug is cocaine base.

76. The method of claim 8, wherein the drug precursor is estrone and the drug is estradiol.